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Docket No.: 025444.1132-US01
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Melton B. Affrime et al.

Application No.: 09/760,588 Group Art Unit: 1614

Filed: January 16, 2001 Examiner: . C. Delacroix-Muirheid

For: TREATING ALLERGIC AND INFLAMMATORY CONDITIONS

TRANSMITTAL LETTER

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Amended Appeal Brief with three appendices (i.e., Appendix A: Claims Appendix; Appendix B: Evidence Appendix (U.S. Patent Appln. Pub. No. US 2003/0004179); Appendix C: Related Proceedings Appendix); and

2. Return receipt postcard.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0740, under Docket No. 025444.1132-US01. A duplicate copy of this paper is enclosed.

It is not believed that extensions of time fees are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit Account No. 50-0740.

Dated: November 3, 2006

Respectfully submitted,

By _____

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For: TREATING ALLERGIC AND INFLAMMATORY CONDITIONS

AMENDED APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under 37 C.F.R. §§ 41.37(a) and (e), an Appeal Brief was filed on April 19, 2006, within six months of the Notice of Appeal filed in this case on November 17, 2005. A Notice of Non-Compliant Appeal Brief was mailed by the Office on October 4, 2006, and Applicants interviewed Examiner Jagoe and Supervisory Patent Examiner Marschel on October 13, 2006. This Amended Appeal Brief is timely filed in response to that Notice and interview.

The fees required under 37 C.F.R. §§ 41.20(b)(2) and 1.17(a) were dealt with in the Transmittal of Appeal Brief that accompanied the submission of the Appeal Brief on April 19, 2006. It is not believed that additional fees or extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional fees or extensions of time are necessary to prevent abandonment

of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including additional fees required for this appeal) are hereby authorized to be charged to our Deposit Account No. 50-0740.

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Appendix A: Claims Appendix

Appendix B: Evidence Appendix (U.S. Patent Appln. Pub. No. US 2003/0004179)

Appendix C: Related Proceedings Appendix

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is:

Schering Corporation (assignee of the present application).

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

On September 29, 2006, Schering Corporation filed a complaint in the United States District Court for the District of New Jersey, alleging infringement of U.S. Patent No. 6,100,274, or both U.S. Patent Nos. 6,100,274 and 6,979,463, by the following defendants: Zydus Pharmaceuticals, USA, Inc.; Sandoz, Inc.; Mylan Pharmaceuticals, Inc.; Orgenus Pharma, Inc.; Orchid Chemicals and Pharmaceuticals, Ltd.; L. Perrigo Co.; Perrigo Co.; Glenmark Pharmaceuticals, Inc., USA; Glenmark Pharmaceuticals, Ltd.; Geopharma, Inc.; Belcher Pharmaceuticals, Inc.; Lupin Pharmaceuticals, Inc.; Lupin, Ltd.; Ranbaxy, Inc.; Rabaxy Laboratories, Ltd.; Dr. Reddy's Laboratories, Inc.; Dr. Reddy's Laboratories, Ltd.; Caraco Pharmaceuticals Laboratories, Ltd.; Sun Pharmaceutical Industries, Ltd.; Watson Pharmaceuticals, Inc.; and Watson Laboratories, Ltd. *Schering Corporation v. Zydus Pharmaceuticals, USA, Inc., et al.,* U.S.D.C. D.N.J., Case No. 3:06-cv-04715-MLC-TJB, filed September 29, 2006.

On October 5, 2006, Schering Corporation filed a complaint in the United States District Court for the Middle District of Florida, Tampa Division, alleging infringement of U.S. Patent No. 6,100,274 by Geopharma, Inc., and Belcher Pharmaceuticals, Inc. *Schering Corporation v. Geopharma, Inc. and Belcher Pharmaceuticals, Inc.*, U.S.D.C. D.Fl., Case No. 8:06-cv-01843-SCB-EAJ, filed October 5, 2006.

On October 5, 2006, Schering Corporation filed a complaint in the United States District Court for the Eastern District of Michigan, alleging infringement of U.S. Patent No. 6,100,274 by Caraco Pharmaceutical Laboratories, Ltd., and Sun Pharmaceutical Industries, Ltd. *Schering Corporation v. Caraco Pharmaceutical Laboratories, Ltd., and*

Sun Pharmaceutical Industries, Ltd. U.S.D.C. E.D.Michigan, Case No. 2:06-cv-14385, filed October 5, 2006.

The application that is the subject of this appeal does not claim priority to either of U.S. Patent Nos. 6,100,274 or 6,979,463. However, U.S. Patent No. 6,100,274 provides the basis for Office Actions, the Final Action and the Advisory Action in the present application.

There are no other prior or pending appeals, interferences, or judicial proceedings that may be related to, will directly affect or will be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are sixteen (16) claims pending in the above-captioned application. Claims 69, 73, 76, 79, 80 and 81 are the independent claims.

B. Current Status of Claims

1. Claims cancelled: 1-68

2. Claims withdrawn from consideration but not cancelled: None

3. Claims objected to: None

4. Claims pending: 69-84

5. Claims allowed: None

6. Claims rejected: 69-84

C. Claims on Appeal

The claims on appeal are claims 69-84.

IV. STATUS OF AMENDMENTS

The Final Rejection was mailed on June 16, 2005. Applicants did not file an Amendment After Final Rejection. On September 16, 2005, Applicants filed a Response After Final Action that did not propose any amendments to any of the claims. Therefore, the claims at issue are those that were presented in the Amendment in Response to Non-Final Office Action, dated March 28, 2005. On October 19, 2005, an Advisory Action Before Mailing of Appeal Brief (hereinafter the "Advisory Action") was mailed. That Advisory Action stated that, for purposes of appeal, the proposed response would be entered in order to remove the rejection under 35 U.S.C. § 112 ¶ 2 (*see* Section VI, below). A Notice of Appeal and a Request for Oral Hearing were filed on November 17, 2005.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention pertains to the administration of desloratadine, a non-sedating antihistamine approved by the Food and Drug Administration.[1] *See, e.g.*, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, enter "desloratadine". Specifically, the present invention provides for oral administration of desloratadine to produce a target steady state serum or pharmacokinetic profile of desloratadine that is therapeutically effective without toxicity. That target steady state pharmacokinetic profile of desloratadine comprises an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose. Appln. No. 09/760,588 (hereinafter "the '588 application" or "the present application"), page 4, lines 11-19; page 20, Table 2; page 21, lines 7-15. This may be achieved, for example, by daily administration of 5 mg of desloratadine for seven days or more. *Id.* at page 18, lines 20-24.

Independent claim 69 is directed to a method of administering a pharmaceutical composition (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) to target a steady state pharmacokinetic profile of desloratadine comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to

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[1] The full chemical name of desloratadine is 8-chloro-6-11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cycloheptic[1,2-b]pyridine. The compound is also known as "DCL" and "descarbonylethoxyloratadine."

maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose. *See* '588 application, page 4, lines 11-19; page 20, Table 2; page 21, lines 7-15.

Independent claim 73 is directed to administering a pharmaceutical composition (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) once a day for about 10 days to target the steady state desloratadine pharmacokinetic profile identified above. *See* '588 application, page 4, lines 11-19; page 18, lines 20-25; page 19, Table 1; page 20, Table 2; page 21, lines 7-15.

Independent claim 76 is directed to administering a pharmaceutical composition (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) for a period of time to target the steady state desloratadine pharmacokinetic profile identified above. *See* '588 application, page 4, lines 11-19; page 18, lines 20-25; page 19, Table 1; page 20, Table 2; page 21, lines 7-15.

Independent claim 79 is directed to a method for achieving a pharmacokinetic profile of desloratadine that is safe and effective for treating nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis and for treating symptoms of chronic idiopathic urticaria in a human 12 years or older. *See* '588 application, page 4, lines 11-19; page 9, lines 8-11; page 31, lines 13-17. This method is carried out by administering a dosage form (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) to target a steady-state pharmacokinetic profile of desloratadine comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose. *See id.*, page 4, lines 11-19; page 20, Table 2; page 21, lines 7-15.

Independent claims 80 and 81 are directed, respectively, to a method of treating nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis in a human 12 years or older, and a method of treating symptoms of chronic idiopathic urticaria in a human 12 years or older. *See* '588 application, page 4, lines 11-19; page 20, Table 2; page 21, lines 7-15. In both claims, this method is safe and effective for treating the relevant symptoms, and is carried out by administering a dosage form (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) to target the steady state pharmacokinetic profile identified above. *See id.*

As explained in Section VII.B, below, an additional basis for appeal is urged for independent claim 73 and dependent claims 74, 75 and 82. Claims 74 and 75 depend from independent claim 73, and dependent claim 82 depends from any of independent claims 79, 80 or 81. Claims 73, 74, 75 and 82 each recite that the method of any of those independent claims is carried out according to a dosage regimen comprising administering, once a day for about 10 days, the desloratadine dosage form specified in those independent claims. *See* '588 application, page 4, lines 11-19; page 18, lines 20-25; page 19, Table 1; page 20, Table 2; page 21, lines 7-15.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the June 16, 2005 Final Rejection, claims 69-84 were rejected under 35 U.S.C. § 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. In the October 19, 2005 Advisory Action, that rejection was determined to have been overcome by Applicants' September 16, 2005 Response After Final Action.

In addition, claims 69-84 were also finally rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,100,274 ("the Kou patent" (commonly owned with the '588 application by Schering Corporation)). In the October 19, 2005 Advisory Action, that rejection was determined not to have been overcome by Applicants' September 16, 2005 Response After Final Action.[2] Accordingly, the rejection under 35 U.S.C. § 102(e) is the ground of rejection to be reviewed on appeal.

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[2] In an interview with the Examiner conducted on August 28, 2006, Applicants indicated that they would be willing to submit a terminal disclaimer to disclaim any term of any patent granted on the present application that would extend beyond the full term of U.S. Patent No. 6,100,274. That terminal disclaimer was submitted on September 5, 2006. In a subsequent telephonic interview, the Examiner informed Applicants that the terminal disclaimer would not remove the rejection of the pending claims under 35 U.S.C. § 102(e).

VII. ARGUMENT

Rejection Under 35 U.S.C. § 102(e) over U.S. Patent No. 6,100,274

A. *Claims 69-72, 76-81, 83-84*

Independent claims 69, 76, 79, 80 and 81, and dependent claims 70-72, 77-78 and 83-84 stand rejected under 35 U.S.C. § 102(e) as anticipated by the Kou patent. In the Final Rejection, the Examiner argues that the Kou patent "discloses administration of a pharmaceutical composition containing an identical compound, i.e., desloratadine, at identical dosages, i.e., 5 mg/day, using applicant's claimed method steps." Final Rejection, page 4. The Examiner concludes that "treatment of nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis as well as chronic idiopathic urticaria in a human 12 years or older would be inherent" and that "one of ordinary skill in the art is able to readily envisage about 10 days of treatment" from the disclosure of the Kou patent. *Ibid.*

The Kou patent teaches stable pharmaceutical compositions comprising desloratadine, a desloratadine-protective amount of a pharmaceutically acceptable basic salt such as calcium dibasic phosphate, and an amount of at least one disintegrant. Column 5, lines 44-54 of the Kou patent states that "the anti-allergic effective amount of [desloratadine] for oral administration" is preferably about 5 to 10 mg/day in single or divided doses, and most preferably 5 mg, once a day. Column 5, lines 49-56 of the Kou patent specifically states:

> Of course the precise dosage and dosage regimen may be varied depending upon the requirements of the patients (e.g., his or her sex, age) as well as the severity of the allergic condition being treated. Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.

> Descarbonylethoxyloratadine possess *[sic]* antihistaminic properties.

1. The Advisory Action. In the Advisory Action, the Examiner reiterates that "[i]t is reasonable to conclude that the same patient is being administered the same composition by the same mode of administration in the same amount in both the instant claims and the Kou reference." Advisory Action, Continuation Sheet. Citing *In re Woodruff*, 16 USPQ 2d 1934, 1936 (Fed. Cir. 1990), the Examiner continues, "[t]he fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on the method." *Id.* The Advisory Action does not contend, however, that the Kou patent discloses any particular steady state pharmacokinetic profile of desloratadine, a steady state pharmacokinetic profile that should be targeted, or how to achieve a steady state pharmacokinetic profile for desloratadine.

The Examiner's reliance on *In re Woodruff, supra,* is misplaced on the law and the facts. First, the rejections upheld in *Woodruff* were under 35 U.S.C. § 103, not, as here, under 35 U.S.C. § 102. Second, contrary to the statement in the Advisory Action, Applicants have not "merely" discovered yet another beneficial effect from the method set forth in the prior art. Rather, they have invented a new method -- that is, administering desloratadine to achieve a specified steady state pharmacokinetic profile of desloratadine that has been found to be safe and effective. This is not explicitly disclosed by the Kou patent, nor is it inherent in that disclosure.

2. The Final Rejection. In the Final Rejection (page 4), the Examiner states:

> The claims are anticipated by Kou because Kou discloses administration of a pharmaceutical composition containing an identical compound, i.e., desloratadine, at identical dosages, i.e., 5 mg/day, using applicant's claimed method steps. Accordingly, treatment of nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis as well as chronic idiopathic urticaria in a human 12 years or older *would be inherent.* (emphasis added)

This statement, however, omits to mention that each of the pending claims in the present application also specifies a steady state pharmacokinetic profile to be targeted by the administration of desloratadine. The Examiner has not and, we believe, cannot explain how the Kou patent discloses, explicitly or inherently, the steady state desloratadine pharmacokinetic profile specified in the claims of the present application.

3. The Standard for Inherent Anticipation. The Examiner has applied the incorrect standard for inherent anticipation. As the Federal Circuit confirmed in *Continental Can Co. v. Monsanto Co.,* 948 F.2d 1264, 1269 (Fed. Cir. 1991), "[i]nherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." The proper test for inherent anticipation is whether the claimed invention "necessarily results from" the disclosure in the allegedly inherently anticipating reference. (*See, e.g., Nicholas v. Perricone, M.D. v. Medicis Pharmaceutical Corporation,* 432 F.3d 1368, 1376-1380 (Fed. Cir. 2005); *Schering Corp. v. Geneva Pharmaceuticals, Inc.,* 339 F.3d 1373, 1381 (Fed. Cir. 2003); and *Rapoport v. Dement,* 254 F.3d 1053, 1062-63 (Fed. Cir. 2001).) These requirements for inherent anticipation as set forth by the Federal Circuit are reflected in the Manual of Patent Examining Procedure. Specifically, MPEP Section 2112, part IV states, "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or

characteristic." MPEP § 2112, part IV (Rev. 5, August 2006) at 2100-47 (emphasis in original).

The Examiner does not explain how practicing the disclosure of the Kou reference would necessarily result in the steady state desloratadine pharmacokinetic profile specified in each of the pending claims of the present application. Instead, the Examiner argues that "one of ordinary skill in the art is able to *readily envisage* about 10 days of treatment from the disclosure of Kou and is therefore anticipated." Final Action, page 4 (emphasis added).

A conclusion of inherent anticipation, however, requires more than an argument that a person of ordinary skill is able to "readily envisage" the claimed invention, as suggested by the Final Rejection. As made clear by the Federal Circuit cases and MPEP provisions cited above, to sustain a conclusion of inherency, an Examiner must find that the extrinsic evidence makes clear that a person of ordinary skill would recognize that "the missing descriptive matter is *necessarily present* in the thing described in the reference." MPEP § 2112, part IV, at 2100-57 (emphasis added). In other words, the Examiner has not explained how that the disclosure of the Kou patent meets the standard required to conclude that it inherently anticipates Applicants' claimed invention.

4. The Absence of Evidence of Inherency. The Final Rejection and the Advisory Action are deficient in another important respect. The MPEP expressly requires the Examiner to provide rationale or evidence tending to show inherency. MPEP § 2112, part IV, at 2100-48. Specifically, the MPEP states, "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily

flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(emphasis in original)." MPEP, *supra* at 2100-48.

In *Ex parte Levy,* the Examiner did not provide objective evidence or cogent technical reasoning to support a conclusion of inherency, and the Board reversed. The same result should obtain here. The Examiner has not provided any objective evidence to support the conclusion of inherency. Nor has the Examiner provided a cogent technical explanation for that conclusion. To the contrary, the Examiner has not provided anything to rebut Applicants' showing that the specified steady state desloratadine pharmacokinetic profile does not, in fact, necessarily result from the disclosure of the Kou patent.

In particular, the Examiner did not address Applicants' argument, in their Response After Final Rejection, that the Kou patent does not discuss how to administer desloratadine in order to achieve an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL. Nor did the Examiner address Applicants' argument that the Kou patent does not discuss how to achieve an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose. Response After Final Rejection, page 5, line 21 - page 6, line 8.

5. Evidence Confirming Absence of Inherency. Beyond failing to provide objective evidence or cogent technical explanation required to sustain an inherency argument, the Examiner has also not addressed Applicants' additional evidence confirming that the Kou patent does not necessarily or inherently disclose the steady state pharmacokinetic profile of the claimed invention. In their Response After Final

Rejection, Applicants cited U.S. Patent Appln. Pub. No. US 2003/0004179 (hereinafter "the Affrime application") for the proposition that the pharmacokinetic profile of desloratadine is variable and can be affected by factors not disclosed in the Kou patent.[3] For example, the Affrime application reports on the results of a clinical trial involving administration of a 5 mg desloratadine tablet to certain adult patients under fasting conditions. Affrime application, ¶¶ 0028 - 0060. The Kou patent, in contrast, does not disclose whether the disclosed 5 mg desloratadine tablet was or is to be administered to patients under fasting conditions, or before or after eating, and does not report any pharmacokinetic data. The Affrime application reports that, under fasting conditions, the administration of a 5 mg tablet of desloratadine resulted in a pharmacokinetic profile with a mean C_{max} of 2.19 ng/mL. Affrime application, Tables 1 and 2 at p. 4. This C_{max} value is only slightly more than half of the arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) value of about 4 ng/mL claimed by Applicants in the present application. Thus, the Affrime application confirms that at least one factor not disclosed in the Kou patent affects the pharmacokinetic profile of people administered 5 mg of desloratadine daily. Therefore, the Affrime application provides further confirmation that the teaching of the Kou patent does not *necessarily* result in the target steady state pharmacokinetic profile of the claimed invention.

For this reason, this case should be guided by the Federal Circuit's decision in *Toro Co. v. John Deere & Co.*, 355 F.3d (Fed. Cir. 2004). In *Toro*, the Federal Circuit

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[3] A copy of the Affrime application is attached at Appendix B, and was included in Applicants' Response After Final Action, filed on September 16, 2005, and was entered into the record by the Examiner in the Advisory Action dated October 19, 2005. The Affrime application, the Kou patent, and the present application are commonly owned by Schering Corporation.

affirmed a District Court finding that the claimed invention was not inherently disclosed by the cited prior art reference. The District Court had found that "no reasonable factfinder could find that one of skill in the art would discern from the [prior art reference] the unique combination of factors" that would necessarily result in the claimed invention." *Id.* at 1319. Likewise in this case, as the Affrime application confirms, there is at least one factor -- namely, the fasting or eating state of the subject -- that cannot be discerned from the Kou patent and that affects the subject's pharmacokinetic profile. Therefore, as in *Toro*, one skilled in the art could not discern from the Kou patent those factors that will necessarily result in the claimed pharmacokinetic profile. Accordingly, the Examiner's finding of inherency cannot properly be maintained.

6. Conclusion. In sum, the Examiner has not provided the required objective evidence or cogent technical explanation of how or why the invention of claims 69-72, 76-81 and 83-84 necessarily results from the teachings of the Kou patent. Nor has the Examiner addressed Applicants' showing that their claimed invention would not, in fact, necessarily result from the Kou patent. The Examiner's finding of inherency therefore should be reversed.

B. ***Claims 73-75 and 82***

1. Additional Basis for Appeal. As described above, independent claim 73 is directed to administering a pharmaceutical composition (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) once a day for about 10 days to target a steady state desloratadine pharmacokinetic profile comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to

maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose. Claims 74 and 75 depend from claim 73, and therefore also require that the pharmaceutical composition be administered "once a day for about 10 days" to target the specified steady state desloratadine pharmacokinetic profile. Claim 82 depends from any of independent claims 79, 80 or 81, and recites that the method of any of those independent claims is carried out according to a dosage regimen comprising administering, once a day for about 10 days, the desloratadine dosage form specified in those independent claims. Applicants urge that the rejection of claims 73-75 and 82 should be reversed for the reasons discussed above with respect to the other pending claims, as well as for the reasons discussed in this section of this brief.

As discussed above, in the Final Rejection's characterization of the Kou patent, the Examiner does not point to any teaching -- because there is none -- of any duration for 5 mg daily administration of desloratadine:

> The claims are anticipated by Kou because Kou discloses administration of a pharmaceutical composition containing an identical compound, i.e., desloratadine, at identical dosages, i.e., 5 mg/day, using applicant's claimed method steps. Accordingly, treatment of nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis as well as chronic idiopathic urticaria in a human 12 years or older *would be inherent.* (emphasis added)

Final Rejection, page 4. Thus, the disclosure in the Kou patent encompasses administration of 5 mg of desloratadine for a single day, or daily administration of 5 mg of desloratadine for any number of days, including periods of less than about seven days. The present application -- not the Kou patent -- teaches that these shorter periods of administration would not necessarily establish the steady state pharmacokinetic profile of the claimed invention.

The Examiner did not contest Applicants' observation that the Kou patent does not disclose or suggest either the pharmacokinetic profile that would result from administering a single desloratadine tablet, or the number of days for which administration of desloratadine is necessary to achieve a steady state pharmacokinetic profile. These features are specifically recited in claims 73-75 and 82 of the present application. The Examiner also has not explained how the claimed steady state pharmacokinetic profile necessarily results from the Kou's patent's express teaching of a variety of doses and dosing regimens, and that the precise dosage and dosage regimen can be modified depending on the requirements of the patients as well as the severity of the allergic condition being treated. Kou patent, col. 5, lines 49-52.

As discussed above, the Examiner's only response to these infirmities in the inherency argument in the Final Rejection is that "one of ordinary skill in the art is able to *readily envisage* about 10 days of treatment from the disclosure of Kou and is therefore anticipated." Final Rejection, page 4 (emphasis added). Anticipation, however, does not follow from a finding that a person of ordinary skill in the art is able "to readily envisage" the claimed invention. Rather, as shown above, a conclusion of inherent anticipation must be supported by a finding that the claimed invention necessarily results from the prior art reference. *See supra*, pp. 15-16. The Examiner has not provided any evidence to support such a finding for any of the application claims, and certainly not for claims 73-75 and 82.

For this reason, as well as for the reasons set forth above with respect to claims 69-72, 76-81, 83-84, the rejection of claims 73-75 and 82 as anticipated under 35 U.S.C. §102(e) by the Kou patent should be reversed, and the Examiner should be directed to

allow all of the pending claims of the present application.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached as Appendix A.

IX. EVIDENCE

As noted above, attached hereto as Appendix B is a copy of U.S. Patent Appln. Pub. No. US 2003/0004179. This document was cited in Applicants' Response After Final Action (37 C.F.R. Section 1.116), filed on September 16, 2005, which was entered into the record by the Examiner in the Advisory Action dated October 19, 2005.

X. RELATED PROCEEDINGS

There are no decisions rendered by a court in any of the judicial proceedings identified in Section II, Related Appeals and Interferences, page 5, above. Accordingly, pursuant to Manual of Patent Examining Procedure § 1205.02, the Related Proceedings Appendix of this brief is included with the indication, "None."

XI. CONCLUSION

Applicants respectfully urge that the rejection of claims 69-84 as being unpatentable under 35 U.S.C. § 102(e) is improper, and that this rejection be reversed.

Dated: November 3, 2006

Respectfully submitted,

By Natalie M. Derzko

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APPENDIX A

CLAIMS

Claims 1-68 (Cancelled).

69. A method of administering a pharmaceutical composition, wherein the method comprises:

administering the pharmaceutical composition, comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, to target a pharmacokinetic (pK) profile for desloratadine comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

70. The method of claim 69, wherein the pharmaceutical composition comprises about 5.0 mg of desloratadine.

71. The method of claim 70, wherein the pharmaceutical composition is administered once a day.

72. The method of claim 69, wherein the desloratadine is in a free base form.

73. A method of administering a pharmaceutical composition, comprising:

administering the pharmaceutical composition, comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, once a day for about 10 days, wherein said administering is carried out to target a pharmacokinetic (pK) profile comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

74. The method of claim 73, wherein the pharmaceutical composition comprises about 5.0 mg of desloratadine.

75. The method of claim 73, wherein the desloratadine is in a free base form.

76. A method of administering a pharmaceutical composition comprising:

administering the pharmaceutical composition, comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, for a period of time to target the establishment of a steady-state pharmacokinetic (pK) profile in the bloodstream of a patient comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

77. The method of claim 76, wherein the pharmaceutical composition comprises about 5.0 mg of desloratadine.

78. The method of claim 76, wherein the desloratadine is in a free base form.

79. A method of achieving a pharmacokinetic (pK) profile of desloratadine that is safe and effective for treating nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis and for treating symptoms of chronic idiopathic urticaria in a human 12 years or older, comprising:

administering a dosage form comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, wherein said administering is carried out to target the pK profile and wherein the pK profile comprises an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

80. A method of treating nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis in a human of 12 years and older comprising:

administering a dosage form comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, wherein said administering is carried out to target a pharmacokinetic (pK) profile that is safe and effective for treating the allergic rhinitis symptoms, and wherein the pK profile comprises an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

81. A method of treating symptoms of chronic idiopathic urticaria in a human of 12 years and older comprising:

administering a dosage form comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, wherein said administering is carried out to target a pharmacokinetic (pK) profile that is safe and effective for treating the chronic idiopathic urticaria symptoms, and wherein the pK profile comprises an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

82. The method of any of claims 79, 80 or 81, wherein said administering is carried out according to a dosage regimen comprising administering the dosage form once a day for about 10 days.

83. The method of any of claims 79, 80 or 81, wherein said dosage form comprises about 5.0 mg of desloratadine.

84. The method of any of claims 79, 80 or 81, wherein the desloratadine is in a free base form.

APPENDIX B

1. Application of Melton B. Affrime, et al., U.S. Patent Appln. Pub. No. US 2003/0004179, included in Applicant's Response After Final Action, filed on September 16, 2005, and entered into the record by the Examiner in the Advisory Action dated October 19, 2005.

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(54) TREATING ALLERGIC AND INFLAMMATORY CONDITIONS

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(57) ABSTRACT

The use of desloratadine for the preparation of a medicament for treating and/or preventing an allergic and inflammatory condition of the skin or upper and lower airway passages in a pediatric patient and a pediatric pharmaceutical composition effective for such treating and/or preventing which comprises an effective amount of desloratadine and a pharmaceutically acceptable carrier are disclosed.

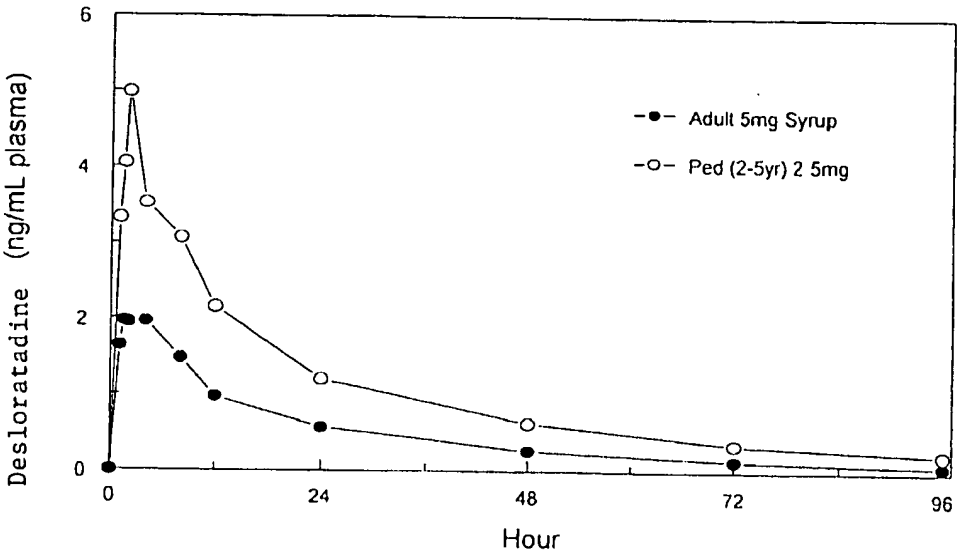
6
4
2
0
Desloratadine (ng/mL plasma)
0
24
48
72
96
Hour
Adult 5mg Syrup
Ped (2-5yr) 2 5mg

Figure 1

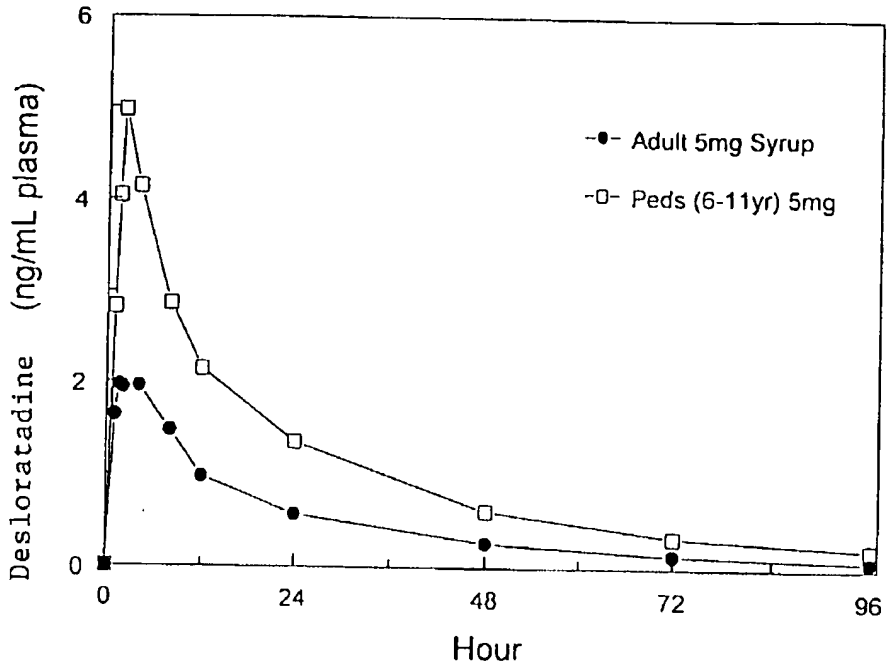
6
4
2
0
Desloratadine (ng/mL plasma)
Adult 5mg Syrup
Peds (6-11yr) 5mg
0
24
48
72
96
Hour

Figure 2

TREATING ALLERGIC AND INFLAMMATORY CONDITIONS

BACKGROUND OF THE INVENTION

[0001] This invention relates to the use of desloratadine for the preparation of a medicament for treating and/or preventing allergic and inflammatory conditions in a pediatric patient and a pediatric pharmaceutical composition comprising an amount of desloratadine effective for such treating and/or preventing.

[0002] Loratadine is disclosed in U.S. Pat. No. 4, 282, 233 as a non-sedating antihistamine useful for treating allergic reactions in animals including humans. The recommended daily dose of loratadine is 10 mg, once daily, for adults and children, 12 years of age and older as well as for children, ages 6 to 11 (in the form of the syrup):.

[0003] Recent Food and Drug Administration ("FDA") proposed regulations would require new drugs to include labeling on how such drugs could be used safely and effectively in pediatric populations. The FDA Modernization Act further addressed the need for improved information about the use of medicines in the pediatric population.

[0004] There is a need for a safe and clinically effective therapy to treat or prevent such allergic and inflammatory conditions of the skin and airway passages in pediatric patients.

SUMMARY OF THE INVENTION

[0005] The present invention provides the use of desloratadine for the preparation of a medicament for treating and/or preventing an allergic and inflammatory condition of the skin or airway passages in a pediatric patient wherein the medicament comprises an effective amount of desloratadine and a pharmaceutically acceptable carrier.

[0006] The present invention also provides a pharmaceutical composition for treating and/or preventing an allergic and inflammatory condition of the skin or airway passages in a pediatric patient which comprises an effective amount of desloratadine and a pharmaceutically acceptable carrier.

[0007] The present invention provides a method of treating and/or preventing an allergic and inflammatory condition of the skin or airway passages in a pediatric patient in need of such treating and/or preventing which comprises administering an amount of desloratadine to the pediatric patient effective for such treating and/or preventing.

[0008] The present invention also provides a method of treating and/or preventing seasonal or perennial allergic rhinitis in a pediatric patient which comprises administering an amount of desloratadine to the pediatric patient effective for such treating and/or preventing.

[0009] The present invention provides a method of treating and/or preventing atopic dermatitis or urticaria in a pediatric patient in need of such which comprises administering an amount of desloratadine to the pediatric patient effective for such treating and/or preventing.

BRIEF DESCRIPTION OF THE FIGURES

[0010] **FIG. 1** graphically displays the variation over time (time zero to 96 hrs) of the mean plasma concentrations of desloratadine (ng/mL of plasma) following (I) a single 5 mL (2.5 mg) dose of desloratadine syrup (0.5 mg/mL) to pediatric volunteers ages 2-5 years and (ii) a single 10 mL (5.0 mg) dose of desloratadine syrup (0.5 mg/mL) to healthy adult volunteers ages 18 to 45 years.

[0011] **FIG. 2** graphically displays the variation over time (time zero to 96 hrs) of the mean plasma concentrations of desloratadine (ng/mL of plasma) following (I) a single 10 mL (5 mg) dose of desloratadine syrup (0.5 mg/mL) to pediatric volunteers ages 6-11 years and (ii) a single 10 mL (5.0 mg) dose of desloratadine syrup (0.5 mg/mL) to healthy adult volunteers ages 18 to 45 years.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The phrase "allergic and inflammatory condition of the skin or airway passages" as used herein means those allergic and inflammatory conditions and symptoms found on the skin and in the upper and lower airway passages from the nose to the lungs. Typical allergic and inflammatory conditions of the skin or upper and lower airway passages include seasonal and perennial allergic rhinitis, non-allergic rhinitis, asthma including allergic and non-allergic asthma, sinusitis, colds (in combination with a NSAID, e.g., aspirin, ibuprofen or APAP) and/or a decongestant e.g. pseudoephedrine), dermatitis, especially allergic and atopic dermatitis, and urticaria and symptomatic dermographism as well as retinophathy, and small vessel diseases, associated with diabetes mellitus.

[0013] The amount of desloratadine effective for treating or preventing allergic and inflammatory conditions of the skin or airway passages will vary with the age, sex, body weight, growth and developmental changes as well as the severity of the allergic and inflammatory condition of the pediatric patient. Typically, the amount of desloratadine effective for treating or preventing such allergic and inflammatory conditions is in the range of about 2.5 mg/day for pediatric patients, ages 6 to less than 12 years, about 1.25 mg/day for pediatric patients, ages 2 to less than 6 years, and about 0.60 to about 0.70 mg/day, preferably about 0.63 mg/day, more preferably about 0.625 mg/day for pediatric patients, ages 6 months to less than 2 years, in single or divided doses, preferably a single daily dose in the form of a syrup.

[0014] Desloratadine is a non-sedating long acting histamine antagonist with potent selective peripheral H1-receptor antagonist activity. Following oral administration, loratadine is rapidly metabolized to descarboethoxyloratadine or desloratadine, a pharmacologically active metabolite. In vitro and in vivo animal pharmacology studies have been conducted to assess various pharmacodynamic effects of desloratadine and loratadine. In assessing antihistamine activity in mice (comparison of ED_{50} value), desloratadine was relatively free of producing alterations in behavior alterations in behavior, neurologic or autonomic function. The potential for desloratadine or loratadine to occupy brain H1-receptors was assessed in guinea pigs following i.p. administration and results suggest poor access to central histamine receptors for desloratadine or loratadine.

[0015] In vivo studies also suggest that an inhibitory effect of desloratadine on allergic bronchospasm and cough can also be expected.

[0016] The clinical efficacy and safety of desloratadine has been documented in over 3,200 seasonal allergic rhinitis patients in 4 double-blinded, randomized clinical trials. The results of these clinical studies demonstrated the efficacy of desloratadine in the treatment of adult and adolescent patients with seasonal rhinitis.

[0017] Efficacy endpoints in all the studies were Total Symptom Score, Total Nasal Symptom Score, Total Non-nasal Symptom Score, and Health Quality of Life (HQOL) analysis in efficacy trials. Desloratadine (5 mg once daily) significantly reduced the total symptom scores (the sum of individual scores for rhinorrhea, sneezing, congestion/stuffiness, nasal itching, itchy/burning eyes, tearing, ocular redness, and itchy ears/palate). Desloratadine (5 mg) was significantly ($p<0.01$) more effective than placebo in reducing nasal symptoms. An important efficacy endpoint analyzed in the desloratadine studies is the AM NOW total symptom score. This parameter measures the total symptom relief by the patient after 24 hours before taking the next day dose. Statistically significant ($p<0.05$) reductions were maintained for the full 24 hour dosing interval over the entire dosage range.

[0018] There were no significant differences in the effectiveness of desloratadine (over the entire dosage range) across subgroups of patients defined by gender, age, or race. Desloratadine is particularly useful for the treatment and prevention of the nasal (stuffiness/congestion, rhinorrhea, nasal itching, sneezing) and non-nasal (itchy/burning eyes, tearing/watery eyes, redness of the eyes, itching of the ears/palate) symptoms of seasonal allergic rhinitis, including nasal congestion, in patients in need of such treating and/or preventing.

[0019] Clinical Study Designs

[0020] Study Treatments

[0021] Subjects were confined to the study site at least 12 hours prior to each treatment administration. In the morning of Day 1 following a 10 hour overnight fast, each subject received one of the following treatments based on his/her subject number and the study period: fasting (Treatment A) or did not eat again (Treatment B) until the 4-hour study procedures were completed, at which time lunch was served. Water was permitted throughout the fasting period except for 2 hours following treatment administration. The subjects remained awake and seated upright/ambulatory for 4 hours post-dose. A physician was present at the time of dosing and remained on site until at least 4 hours post-dose. Subjects were under medical supervision throughout their confinement at the study site. Each treatment administration was separated by at least a 7 day washout period.

[0022] Pharmacokinetics

[0023] Blood samples were collected for determination of the plasma pharmacokinetic profile of desloratadine. Fifteen milliliters (15 mL) of blood were collected just prior to drug administration (0 hour) and at pre-specified times after dosing in both periods. All blood samples were collected into heparin-containing tubes at the specified times. The blood samples were centrifuged within 30 minutes after collection for 20 minutes at approximately 4° C. and at approximately 3000 rpm. The plasma was separated and transferred into two separate appropriately labeled tubes, frozen to at least −20° C. and maintained in the frozen state until assayed for desloratadine content.

[0024] The plasma concentration data for desloratadine were used to estimate the following pharmacokinetic parameters using standard methodologies well known to those skilled in the art.

[0025] The major pharmacokinetic variables of interest were the plasma AUC and Cmax. All plasma samples were assayed for desloratadine concentrations using a validated method such as gas/liquid chromatography with a NP detector(GLC/NPD). The validation of the assay methods included documentation of its selectivity, limit of quantitation, linearity, precision and accuracy. The lower limit of quantitation (LOQ) of the assay was established at 0.1 ng/mL for desloratadine.

[0026] Safety Measurements Assessed

[0027] For safety evaluation, physical examinations, vital signs, electrocardiograms and clinical laboratory tests were conducted at screening and at the conclusion of the study. In addition, vital signs were monitored prior to treatment administration and daily during both treatment periods. Additional clinical laboratory tests and ECGs were obtained prior to dosing in each treatment period. The assessment, severity and relationship to treatment of adverse events were evaluated.

Study No. 1

[0028] The objective of this study was to evaluate the effect of food on the bioavailability of desloratadine. These adult studies were designed to define the bioavailability/bioequivalence (BA/BE) relative to the tablet formulation, the effect of food on the pharmacokinetics following administration of the syrup formulation and the pharmacokinetic profile of desloratadine after single dose administration of the syrup to healthy male and female adult subject.

Single-Dose BA/BE Study

[0029] This was a Phase I, randomized, open-label, three-way crossover study in 30 healthy adult subjects (ages 18 to 45) who received a 5 mg desloratadine tablet and 10 mL of desloratadine syrup (0.5 mg/mL) under fasted conditions as well as following a high-fat, high-calorie breakfast on three separate occasions.

[0030] Subjects were confined at the study site at least 12 hours prior to each treatment (Day-1). In the morning of Day 1 following a 10 hour overnight fast, each subject received one of the following treatments based on his/her subject number and the study period:

[0031] Treatment A: One desloratadine (DL) 5 mg tablet administered after a 10 hour fast.

[0032] Treatment B: Ten (10) mL of DL syrup (0.5 mg/mL) following a 10 hour fast

[0033] Treatment C: Ten (10) mL DL syrup (0.5 mg/mL) administered immediately following a standardized high-fat, high caloric breakfast.

[0034] Subjects randomized to receive the standardized high-fat, high caloric breakfast (Treatment C) consumed the prescribed meal in a 20-minute period prior to drug admin-

istration and received the appropriate dose of desloratadine within 5 minutes after completing the breakfast.

[0035] Study Population/Inclusion Criteria/Exclusion Criteria.

[0036] Inclusion Criteria:

[0037] Subjects were males or females between the ages of 18 and 45 years inclusive, and had a Body Mass Index (BMI) between 19-27.

[0038] Clinical laboratory tests (CBC, blood chemistries, urinalysis) were within normal limits or clinically acceptable to the Investigator/Sponsor.

[0039] Drug screen for drugs with a high potential for abuse were negative at screening and on admission to the study site.

[0040] Subjects were free of any clinically significant disease that required a physician's care and/or may have interfered with study evaluations, procedures or participation.

[0041] Subject gave written informed consent (prior to any study-related procedures being performed) and were willing to adhere to restrictions and examination schedules.

[0042] Subjects had a normal or clinically acceptable physical examination and ECG.

[0043] Exclusion Criteria:

[0044] Subjects who had a history of any clinically significant local or systemic infectious disease within four weeks prior to initial treatment administration.

[0045] Subjects who did not comply with the requirement that he or she should not have used any drugs (except acetaminophen) within 14 days prior to the study nor alcohol or xanthine-containing substances with 72 hours prior to study drug administration.

[0046] Subjects who had participated in a clinical trial of any investigational drug within 30 days prior to the start of the study.

[0047] Subjects who were, or were known to be former, narcotic addicts or alcoholics.

[0048] Subjects who were positive for hepatitis B surface antigen or hepatitis C antibody.

[0049] Subjects who were positive for HIV antibodies.

[0050] Subjects who had a clinically significant history of food or drug allergy.

[0051] Subjects who had a known allergy or intolerance to loratadine.

[0052] Subjects who smoked, used tobacco products or used an adjunct to smoking cessation within the past 6 months (positive urine test).

[0053] Females who were not surgically sterilized or were considering reversal of their surgical sterilization or were not at least 1 year post-menopausal.

[0054] Females who had a positive urine pregnancy test at screening or on admission to the study site.

[0055] Females who were lactating.

[0056] Study Treatments

[0057] Subjects were confined to the study site at least 12 hours prior to each treatment administration. In the morning of Day 1 following a 10-hour overnight fast, each subject received one of the following doses.

[0058] Each dose was administered with 180 mL (6 fl oz) of non-carbonated room temperature water. The tablet was swallowed whole, not chewed or crushed. After dosing, the oral cavity will be inspected to assure that the subject had swallowed the tablet/syrup. For subjects randomized to Treatment B or Treatment C the study medication was administered by having the volunteer drink the entire 10 mL of desloratadine syrup, followed by two 10 mL tap water rinses of the dose container (i.e., oral syringe, etc.) to ensure complete dose intake. Subjects continued fasting (Treatment A and B) or did not eat again (Treatment C) until the 4-hour study procedures were completed, at which time lunch was served. Water was permitted throughout the fasting period except for 2 hours following treatment. The subjects remained awake and seated upright/ambulatory for 4 hours post-dose.

[0059] All subjects were confined to the study site until the 120-hour blood samples, vital signs and laboratory tests were obtained. No strenuous physical activity was permitted, and the subjects were not allowed visitors while they were confined to the study site. A washout period of at least 14 days separated each period of the study.

[0060] The mean pharmacokinetic profiles of desloratadine following single dose administration of the syrup formulation under fasted conditions are illustrated in **FIG. 1**.

Study No. 2

[0061] Single-Dose PHARMACOKINETICS in Pediatric Subjects (≧2 to <6 Years Old)

[0062] The objective of this open label study was to characterize the pharmacokinetic profile of desloratadine and 3-OH desloratadine following a single dose of 5 mL (2.5 mg) desloratadine syrup (0.5 mg/mL) administered orally to healthy pediatric subjects ranging in age from ≧2 to <6 years. These pediatric subjects were found to have normal or clinically acceptable laboratory tests be free of any clinically significant disease and to have normal or clinically acceptable ECGs.

[0063] A total of 18 healthy pediatric subjects (12 males and 6 females) with at least 4 subjects in the following age groups: ≧2 but <3, ≧3 but <4, ≧4 but <5, ≧5 but <6 were enrolled and successfully completed this open-label, single-center study. In this study, each subject received a single 5 mL (2.5 mg) dose of desloratadine syrup (0.5 mg/mL) administered orally.

[0064] Subjects were screened within 3 weeks of dosing, and those who met the entry criteria were confined to the study center within 24 hours prior to dosing. Upon confinement, the clinical laboratory safety tests performed at Screening were repeated for each subject. The next morning all subjects received the study medication. Vital signs were

obtained daily. Blood samples were collected at pre-specified times before and after dosing for safety and pharmacokinetic evaluations. Subjects were continually observed and questioned throughout the study for the possible occurrence of adverse events. Subjects were also instructed to report any unusual experiences or discomfort. No strenuous physical activity was permitted, and the subjects were not allowed visitors (besides the parents or legal guardians) while they were confined to the study site. Following the 24-hour study-related procedures for safety and pharmacokinetic evaluations, subjects were dismissed from the study site. They returned to the study site on Days 3, 4 and 5 for the 48-hour, 72-hour and 96-hour study-related procedures. Following completion of all study-related procedures on Day 5, subjects were discharged from the study.

[0065] The mean plasma concentration-time (0-96 hrs) profiles of desloratadine following administration of desloratadine to pediatric subjects ≧2 to <6 years old and adults 18 to 45 years old are illustrated in **FIG. 1**.

[0066] The derived pharmacokinetic parameters are provided in Table 1.

TABLE 1

Mean Pharmacokinetic Parameters
The Mean (% CV) Pharmacokinetic Parameters of Desloratadine Following Oral, Single-Dose Administration of 5.0 & 2.5 mg of Desloratadine under Fasted Conditions:

		Mean (% CV)[1]	
Syrup Data	N	Cmax(ng/mL)	AUC(96)(ng · hr/mL)
Adults(5 mg)	30	2.19	45.2
Pediatrics(≧2 to <6 yr, 2.5 mg)	18	5.36	98.6

[1]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

[0067] Single oral doses of 5 mL (2.5 mg) of desloratadine syrup administered to healthy pediatric volunteers ≧2 to <6 years of age was safe and well tolerated. To obtain similar systemic exposure in pediatric subjects (≧2 to <6 years of age) as found in adults administered a 5 mg dose, the 2.5 mg dose should be reduced by 50% to 1.5 mg (See Study No. 4).

Study No. 3

[0068] Single-Dose PHARMACOKINETICS in Pediatric Subjects (24 6 to <12 Years Old)

[0069] This open-label study in 18 healthly pediatric subjects was designed to characterize the pharmacokinetic profile of desloratadine and 3-OH desloratadine following a single 2.5 mg (5 mL) dose of desloratadine syrup administered orally to healthy pediatric volunteers ranging in age from ≧6 to <12 years. These pediatric patients were found to have normal or clinically acceptable laboratory tests be free of any clinically significant disease and to have normal or clinically acceptable ECGs.

[0070] The objective of this study was to characterize the pharmacokinetic profile of desloratadine following a single dose of 10 mL (5 mg) desloratadine syrup (0.5 mg/mL) administered orally to healthy pediatric subjects ranging in age from ≧6 to <12 years.

[0071] A total of 18 healthy pediatric subjects (9 males and 9 females) with at least 3 subjects in the following age groups: ≧6 but <7, ≧7 but <8, ≧8 but <9, ≧9 but <10, ≧10 but <11, and ≧11 but <12 were enrolled and successfully completed this open-label, single-center study. In this study, each subject received a single 10 mL (5 mg) dose of desloratadine syrup (0.5 mg/mL) administered orally.

[0072] Subjects were screened within 3 weeks of dosing, and those who met the entry criteria were confined to the study center within 24 hours prior to dosing. Upon confinement, the clinical laboratory safety tests performed at Screening were repeated for each subject. The next morning all subjects received the study medication. Vital signs were obtained daily. Blood samples were collected at pre-specified times before and after dosing for safety and pharmacokinetic evaluations. Subjects were continually observed and questioned throughout the study for the possible occurrence of adverse events. Subjects were also instructed to report any unusual experiences or discomfort. No strenuous physical activity was permitted, and the subjects were not allowed visitors (besides the parents or legal guardians) while they were confined to the study site. Following the 24-hour study-related procedures for safety and pharmacokinetic evaluations, subjects were dismissed from the study site. They returned to the study site on Days 3, 4 and 5 for the 48-hour, 72-hour and 96-hour study-related procedures. Following completion of all study-related procedures on Day 5, subjects were discharged from the study.

[0073] The mean plasma concentrations of desloratadine following administration of (i) a single 5 mL (2.5 mg) dose of desloratadine syrup (0.5 mg/mL) to pediatric subjects (ages ≧6 to <12) and (ii) a single 10 mL (5.0 mg) dose of desloratadine syrup (0.5 mg/mL) to adult subjects (ages 18 to 45).

[0074] The derived pharmacokinetic parameters are provided in Table 2.

TABLE 2

Mean Pharmacokinetic Parameters
The Mean (% CV) Pharmacokinetic Parameters of Desloratadine Following Oral, Single-Dose Administration of 5.0 mg of Desloratadine under Fasted Conditions:

		Mean (% CV)[1]	
Syrup Data	N	Cmax(ng/mL)	AUC(96)(ng · hr/mL)
Adults(5 mg)	30	2.19	45.2
Pediatrics(≧6 to <12 yr, 5.0 mg)	18	5.3	101

[1]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

[0075] Single oral doses of desloratadine syrup administered to healthy pediatric subjects ≧6 to <12 years of age was safe and well tolerated. To obtain similar systemic exposure in pediatric subjects (≧6 to <12 years of age) as in adults administered 5 mg, the dose should be reduced by 50% to 2.5 mg (See Study No. 5).

[0076] Based on the findings of the studies pharmacokinetic studies will be repeated in pediatric subjects between the ages of ≧2 to <6 years and ≧6 to <12 years.

Study No. 4

[0077] Single Dose Pharmacokinetics of Desloratadine Syrup in Healthy Pediatric Volunteers 2-5 Years of Age

[0078] Study Objective:

[0079] The objective of this open label study will be to characterize the pharmacokinetic profile of desloratadine following a single dose of 2.5 mL (1.25 mg) desloratadine syrup (0.5 mg/mL) administered orally to healthy pediatric subjects ranging in age from ≧2 to <6 years. These pediatric subjects selected for inclusion into this open label study should have normal or clinically acceptable laboratory tests, be free of any clinically significant disease and have normal or clinically acceptable ECGs.

[0080] Study Design:

[0081] A total of eighteen (18) healthy male or female pediatric volunteers—with at least three subjects at each age stratification—will receive a single dose of 2.5 mL (1.25 mg) of desloratadine syrup (0.5 mg/mL) administered orally. The protocol of Study No. 2 will be followed.

[0082] Study Endpoints:

[0083] The following pharmacokinetic parameters will be obtained from the resulting desloratadine concentration-time profiles:

[0084] Area under the concentration-time curve ($AUC_{0-\infty}$, AUC_{0-t})

[0085] Peak concentration (C_{max})

[0086] Time to peak concentration (T_{max})

Study No. 5

[0087] Single Dose Pharmacokinetics of Desloratadine Syrup in Healthy Pediatric Volunteers ≧6 to <12 Years of Age

[0088] Study Objective:

[0089] The objective of this open label study will be to characterize the pharmacokinetic profile of desloratadine and 3-OH desloratadine following a single dose of 5.0 mL (2.5 mg) desloratadine syrup (0.5 mg/mL) administered orally to healthy pediatric subjects ranging in age from ≧6 to <12 years. These pediatric patients selected for inclusion into this open label study should have normal or clinically acceptable laboratory tests, be free of any clinically significant disease and have normal or clinically acceptable ECGs.

[0090] Study Design:

[0091] A total of eighteen (18) healthy male or female pediatric volunteers ages from ≧6 to <12 years—with at least three subjects at each age stratification will receive a single dose of 5 mL (2.5 mg) desloratadine syrup (0.5 mg/mL) administered orally. The protocol of Study No. 3 will be followed.

[0092] Study Endpoints:

[0093] The following pharmacokinetic parameters will be obtained from the resulting desloratadine concentration-time profiles:

[0094] Area under the concentration-time curve ($AUC_{0-\infty}$, AUC_{0-t})

[0095] Peak concentration (C_{max})

[0096] Time to peak concentration (T_{max})

[0097] U.S. Pat. No. 4,659,716 discloses methods of making desloratadine, pharmaceutical compositions containing it and methods of using desloratadine and pharmaceutical compositions containing it to treat allergic reaction in mammals.

[0098] U.S. Pat. No. 5,595,997 discloses pharmaceutical compositions containing desloratadine and methods of using desloratadine for treating and preventing various disease states, e.g., allergic rhinitis.

[0099] Desloratadine is available from Schering Corporation, Kenilworth, N.J.

[0100] The desloratadine syrup (0.5 mg/ml) is disclosed in International Patent Application PCT/US99/10469 having an international application date of May 27, 1999.

[0101] The pharmaceutical compositions of desloratadine can be adapted for any mode of administration e.g., for oral, parenteral, e.g., subcutaneous ("SC"), intramuscular ("IM"), and intraperitoneal ("IP"), topical or vaginal administration or by inhalation (orally or intranasally). Preferably desloratadine is administered orally.

[0102] Such pharmaceutical compositions may be formulated by combining desloratadine or an equivalent amount of a pharmaceutically acceptable salt thereof with a suitable, inert, pharmaceutically acceptable carrier or diluent that may be either solid or liquid. Desloratadine may be converted into the pharmaceutically acceptable acid addition salts by admixing it with an equivalent amount of a pharmaceutically acceptable acid. Typically suitable pharmaceutically aceptable acids include the mineral acids, e.g., HNO_3, H_2SO_4, H_3PO_4, HCl, HBr, organic acids, including, but not limited to, acetic, trifluoroacetic, propionic, lactic, maleic, succinic, tartaric, glucuronic and citric acids as well as alkyl or arylsulfonic acids, such as p-toluenesulfonic acid, 2-naphthalenesulfonic acid, or methanesulfonic acid. The preferred pharmaceutically acceptable salts are trifluoroacetate, tosylate, mesylate, and chloride. Desloratadine is more stable as the free base than as an acid addition salt and the use of the desloratadine free base in pharmaceutical compositions of the present invention is more preferred.

[0103] Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pa.

[0104] Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Solid form preparations may be converted into liquid preparations shortly before use for either oral or administration. Parenteral forms to be injected intravenously, intramuscularly or subcutaneously are usually in the

form of sterile solutions and may contain tonicity agents (salts or glucose), and buffers. Opacifiers may be included in oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

[0105] Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g., nitrogen.

[0106] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, syrups suspensions and emulsions.

[0107] Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

What is claimed is:

1) The use of desloratadine for the preparation of a medicament for treating and/or preventing an allergic and inflammatory condition of the skin or airway passages in a pediatric patient wherein the medicament comprises an effective amount of desloratadine and a pharmaceutically acceptable carrier.

2) A pharmaceutical composition for treating and/or preventing an allergic and inflammatory condition of the skin or airway passages in a pediatric patient which comprises an effective amount of desloratadine and a pharmaceutically acceptable carrier.

3) The use or pharmaceutical composition of claim 1 or 2 wherein the pediatric patient is 6 to less than 12 years of age and the effective amount of desloratadine is about 2.5 mg/day.

4) The use or pharmaceutical composition of claim 1 or 2 wherein the pediatric patient is 2 to less than 6 years of age and the effective amount of desloratadine is about 1.25 mg/day.

5) The use or pharmaceutical composition of claim 1 or 2 wherein the pediatric patient is about 6 months to less than 2 years of age and the effective amount of desloratadine is about 0.60-0.70 mg/day.

6) The use or pharmaceutical composition of claim 1 or 2 wherein the allergic and inflammatory condition of the skin or airway passages is season allergic rhinitis, perennial allergic rhinitis, atopic dermatitis, urticaria or allergic asthma.

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